LETTERS

Antibodies to GAD in Diabetic Patients with Chronic Hepatitis C

There is a documented relationship between hepatitis C virus (HCV) infection and evidence of autoimmune thyroid disease. (AITD).[1] Furthermore titres of glutamic acid decarboxylase (GAD) antibodies, one of the markers for autoimmune insulitis, are higher in patients with AITD than in controls.[2] We have therefore examined the status of antithyroid and GAD antibodies in diabetic patients with chronic hepatitis C.

Sera from 63 diabetic patients (46 men and 17 women; mean age, 62.2 ± 8.9 years), all with chronic hepatitis C diagnosed serologically and histologically were tested for anti-GAD and anti-thyroid (anti-thyroglobulin and anti-microsomal) autoantibodies. The diagnosis of diabetes was established, following a 75g oral glucose tolerance test, based on the guidelines of the World Health Organization, and Type 1 diabetic patients were not included. No patient had received interferon. GAD antibodies were measured by a radioimmunoassay (RIA) kit using human recombinant GAD 65 as an antigen (RSR Limited, Cardiff, UK) (anti-thyroglobulin antibodies by a particle agglutination test (PA) or a RIA and anti-microsomal antibodies detected by a PA.

Eight of 46 (17.4 %) men and 4 of 17 (23.5 %) women had anti-thyroid autoantibodies. One of the men and 2 of the women had subclinical hypothyroidism, and 1 woman had hyperthyroidism. Anti-GAD antibodies were however under measurable range (i.e. 1.3 U ml^{-1}) in all patients.

Hieronimus *et al.*[3] have recently reported that only 1 of 47 chronic hepatitis C patients, a known case of Type 1 DM, had anti-GAD antibodies. In this study, we have found no anti-GAD antibodies in diabetic patients with hepatitis C, even in patients with AITD. Although the number of subjects was small, these results suggest that HCV rarely contributes to the occurrence of GAD antibodies. However, it is now well recognized that interferon therapy for chronic viral hepatitis can precipitate IDDM.[4] Further study is needed to clarify whether interferon may induce the occurrence of GAD antibodies preferentially in chronic HCV-infected patients.

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A Combined Treatment for Severe Diabetic Neuropathy Symptoms

Diabetic neuropathy is a common complication of diabetes and a major factor leading to foot ulceration and amputation. Clinically significant neuropathy has been reported to occur in 23 % of patients with Type 1 and 32 % with Type 2 diabetes.[1] Severe diabetic neuropathy may present with acute or chronic painful peripheral sensory neuropathy, both particularly difficult to treat and only partially responsive to current therapy.[2] We describe an apparently effective combination therapy for these conditions. The combination consists of the conventionally used tricyclic antidepressants, preferably Lofepramine, in combination with L-phenylalanine and vitamin B_{12}.[3]

The treatment was used in a total of 14 patients, all with chronic painful neuropathy previously unresponsive to conventional therapy, with good effect in 13. Vitamin B12 deficiency was excluded prior to therapy. We present two case reports. One was a 28-year-old patient with Type 1 diabetes who had had severe hyperaesthesia since 1989. Electromyography was consistent with severe diabetic neuropathy. She was on 200 mg morphine daily in combination with trazodone and ephedrine without control and had twice been admitted for treatment with IV lignocaine. Prior to our combined medication, she had been wheelchair bound. A regimen of 70 mg Lofepramine and 500 mg L-phenylalanine both twice daily, with weekly 1 mg vitamin B12 injections resulted in a pain free and normally active life. Six months into treatment, she continued to respond well.

A 48-year-old male, diagnosed as having Type 2 diabetes when 28, first described symptoms of diabetic neuropathy when aged 40, which increased in severity over several years, including severely painful neuropathy with spasm, diabetic amyotrophy, and numbness and loss of vibration sense in the extremities. Electromyography was consistent with diabetic neuropathy. Treatment with tricyclic antidepressants alone was ineffective. Treatment with our combined therapy significantly improved reported symptoms within 12 hours. Almost complete clinical resolution of his chronic symptoms had occurred after 1 week. The patient continues to respond to the therapy while taking the medication.

A further 11 patients with severe diabetic neuropathy have responded well to the therapy. No significant side-effects were reported, although one patient experienced a mild transient sinus tachycardia. Cardiac status, therefore, should be monitored in patients with significant cardiovascular disease. All responses began within 72 hours of starting therapy. Four have required continued therapy, while in the remainder remission has to date occurred after a course of 6 weeks and therapy is no longer required.

Tricyclic antidepressants inhibit noradrenaline reuptake, and their actions appear clinically to be augmented by the noradrenaline precursor, L-phenylalanine, and vitamin B12, an essential cofactor in axonal enzymatic pathways, which is involved in neuronal noradrenaline metabolism. The noradrenergic effects of tricyclic antidepressants are thought to act by modulating neurogenic pain gating,[2] apparently enhanced by addition of L-phenylalanine and vitamin B12. Our cases suggest the effect of this combined therapy on the symptoms of severe diabetic neuropathy are considerable. Double blind, placebo controlled studies using quantitative neural function tests are being undertaken. Severe neuropathic conditions are distressing, insidious, expensive, and difficult to treat,[4] therefore a novel effective therapy would be gratefully welcomed.

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Parental Hypertension and Risk of Diabetic Nephropathy

Roglic *et al*.[1] report a weak association between a parental history of hypertension and the presence of microalbuminuria in the EURIODIAB cohort, citing an odds ratio of 1.3 for the risk of albuminuria in those with and without a parental history of hypertension. By contrast, Krolewski *et al*.[2] have suggested that the influence of parental hypertension is far more powerful, reporting an odds ratio of 3.4 for the likelihood of nephropathy in the presence of parental history of hypertension. There are methodological differences between these studies, not least the difference in the degree of renal disease. As discussed by Roglic,[1] some of their subjects with microalbuminuria may not later progress to overt nephropathy.

We examined parental history of hypertension in 118 patients with Type 1 diabetes and established nephropathy. The patients had advanced renal disease: 87 (74 %) receiving renal replacement therapy (either transplant or dialysis) and a further 31 (26 %) had serum creatinine of greater than 120 μmol l^{-1} with elevated urinary albumin concentration ($>$ 300 mg l^{-1}). We compared these cases to a control group of 118 Type 1 patients of at least 14 years duration of diabetes, without evidence of microalbuminuria or nephropathy and matched for age, sex, and diabetes duration.

In our group 32 % of those with nephropathy compared to 27 % of controls had at least one parent with a history of hypertension (Fisher's exact test P = NS). Thus, in a group of patients with more severe renal disease the influence of a parental history of hypertension is still not particularly marked. We support the conclusions of Roglic *et al*. and suggest that inherited factors other than hypertension may explain the influence of family history on diabetic renal disease.

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